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Research Paper

Study on correlation between C-reactive protein and gestational diabetes mellitus

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Abstract

Objective: To investigate correlation between C-reactive protein(CRP) and gestational diabetes mellitus(GDM). **Methods:**Twenty-five GDM women were served as study group, and thirty normal pregnant women were selected as control group. The serum FPG, 2hPG, HbA1c and CRP levels and the leukocyte count were detected in the two groups, in order to observe the relationship between gestational diabetes mellitus and inflammatory markers. **Results:**The age and gestational week did not show difference in the two groups($P > 0.05$). But there was a significant difference in body mass index(BMI) between the GDM group and the control group($P < 0.05$). The serum FPG, 2hPG, HbA1c and CRP levels and the leukocyte count in the GDM group were higher than those in the control group, and the difference was significant($P < 0.05$). There was positive correlation between serum C-reactive protein value and FPG, 2hPG, HbA1c serum levels or the leukocyte count in GDM group. But in the control group there was no correlation between them. **Conclusion:**The results suggest that there is correlation between C-reactive protein and gestational diabetes mellitus, and inflammation may play an important role in the development of gestational diabetes mellitus.

Key words: C-reactive protein; diabetes; gestational; inflammation

INTRODUCTION

Gestational diabetes mellitus(GDM), a real threat to maternal and fetal health, complicates 3%~5% of pregnancies. GDM is defined by the third international workshop-conferences on gestational diabetes as the new onset or new diagnosis of glucose intolerance during pregnancy[1]. Women with a history of GDM have an 18%-50% risk of developing type 2 diabetes mellitus (T2DM) within 5 years following pregnancy[2]. The mechanisms involved in the development of GDM are not completely understood. It is a hypothesis that GDM may be a systemic inflammation mediated by cytokine, similar to immune disease[3]. A new research reports that C-reactive protein(CRP) as an inflammatory factor is associated strictly with the physiology and pathology of pregnancy, and the rise of serum CRP level can provide related theoretical basis for them[4]. C-reactive protein induces insulin resistance(IR), a state in which a given concentration of insulin produces a less-than-expected biological effect by inflammatory effect[5]. We examined the serum FPG, 2 hPG, HbA1c and CRP levels and the leukocyte count in the normal pregnant group and the GDM group, in order to observe the association between CRP and GDM risk, and to provide some effective assessment for its early detection, prevention and clinical treatment.

MATERIALS AND METHODS

Subjects

Fifty-five single pregnancies divided into two groups were recruited from our division's outpatient or inpatient service between June 2006 and January 2007. Thirty age-matched mid and late trimester gravida without any risk factors for diabetes and with normal

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glucose tolerance during and after pregnancy served as the control group(NGT). Others served as the GDM group. All subjects were excluded from smoking or alcohol abuse and drugs interfering glycometabolism and lipometabolism. Complications and diseases such as hypertension, liver or kidney diseases, disorders of other endocrine glands such as hyperthyroidism were excluded, too.

Diagnostic criteria

Women were defined as having normal glucose tolerance(GLT) in pregnancy if they had undergone a 50g glucose-loading test between 24 and 28 weeks' gestation with free blood glucose(FBG) level less than 5.6 mmol/L and 1 h postprandial blood glucose(PBG1h) level less than 7.8 mmol/L. Women whose PBG1h level was above 7.8 mmol/L were considered to be at increased risk for GDM and underwent an oral glucose tolerance test(OGTT) with 75g glucose load within 1-2 weeks following the GLT. GDM was diagnosed following the criteria of the American National Diabetes Data Group (NDDG) using OGTT: fasting glucose, 5.8 mmol/L; 1 h glucose, 10.6 mmol/L; 2 h glucose, 9.2 mmol/L; and 3 h glucose, 8.1 mmol/L[6]. These criteria require subjects to have at least two values equaling or exceeding the following cutoff points after administration of a 75 g glucose load.

Laboratory measurements

On the day of the OGTT, demographic and historical information, including the age, the numbers of preceding pregnancies, the duration of gestation, personal medical, obstetrical, and smoking history and family history was collected by interviewer-administered questionnaire. Weight and height were measured. BMI was computed as prepregnant weight for height (weight in kilograms divided by the square of height in meters).Venous blood samples were drawn on the morning after overnight fast, kept at room temperature and never thawed before the testing. Assays for serum FPG, 2 hPG, HbA1c and CRP levels and the leukocyte count were performed as routine clinical tests by hospital laboratory staff. Glucose was measured by the hexokinase glucose-6-phosphate dehydrogenase method. Serum CRP levels were measured by automated nephelometric immunoassay using the Beckmancoulter SYNCHRON LX-20 (Beckman Coulter, Inc. America). White blood cell was counted by Sysmex XT 1800I Blood Analysis Instrument. Additionally, concentration of glycosylated haemoglobin(HbA1c) was calculated by means of ion-exchange chromatography method employing chromatographic-spectrophotometric test (BioSystems, Spain).

Statistical analysis

All statistical analyses were done using the SPSS version 11.0. Data are presented as Mean $\pm s$. The data from the two groups were compared using paired *t* tests for normally distributed data. Associations between continuous variables are described by correlation coefficients(Pearson). In all tests, significance was assumed when $P < 0.05$.

RESULTS

Baseline data

Characteristics of the subjects are presented in ***Tab 1***. There were no significant differences between the groups in age and gestational week. Otherwise, there was a significant difference in body mass index(BMI) mean values between the GDM group and the NGT group($P < 0.05$).

Inflammatory markers and serum glucose level

Compared with the control group, women with a history of GDM had higher levels of serum FPG, 2 hPG, HbA1c and CRP levels and the leukocyte count(all $P < 0.05$; ***Tab 2***). There was positive correlation between serum C-reactive protein value and FPG, 2hPG, HbA1c serum levels or the leukocyte count in GDM group(r = 0.40, 0.42, 0.35, 0.38). But in the control group there was no correlation between them.

Tab 1 **Comparison of baseline data between two groups** ($\bar{x} \pm s$)

Group	*n*	age	gestational week	prepregnancy BMI (kg/m^2)	current BMI (kg/m^2)
NGT	30	27.4 ± 3.6	27.1 ± 2.4	21.5 ± 2.1	24.7 ± 5.1
GDM	25	25.4 ± 4.2	26.8 ± 3.0	25.8 ± 4.5*	27.8 ± 5.9*

*Compared with NGT, $P < 0.05$.

Tab 2 **Comparison of inflammatory markers and serum glucose level** ($\bar{x} \pm s$)

Item	NGT	GDM
FPG(mmol/L)	4.40 ± 0.6	4.90 ± 0.7
2hPG(mmol/L)	7.20 ± 1.2	10.2 ± 1.5
HbA1c(%)	5.90 ± 2.1	7.30 ± 2.7**
WBC($\times 10^9$/L)*	5.02 ± 1.56	7.28 ± 2.61
CRP(mg/L)	4.70 ± 1.2	7.30 ± 2.8**

*Statistical analysis according to its natural logarithm. Compared with NGT, **$P < 0.05$.

DISCUSSION

Acute phase protein, including the complement system, blood coagulation, the fibrinolytic system, antiprotease, transfer protein and sialic acid(widely used as a marker of disease activity) is the protein whose serum concentration elevates or descends 25 percent in inflammatory conditions. Acute phase protein, produced

by the liver, is a fast started organismal defence mechanism, which can discriminate phospholipids of some pathogen and impaired cells, activate the complement system and clear target cells by interaction between humoral immunity and cellular immunity. C-reactive protein(CRP), the predominant and sensitive marker in acute phase response, with a minimal serum concentration of below 8 mg/L in health adult, elevates obviously during acute inflammation, trauma and other diseases[7]. Its synthesis is regulated by activated monocyte, fibroblast and some cytokines such as interleukin(IL), tumor necrosis factor(TNF-α) and transforming growth factor(TGF-β), especially IL-6[8].

The development of GDM is due to the increasingly augmented insulin resistance following gravid progression, which urges organism to need more requisite amount of insulin secretion. Women with GDM always have beta cells of pancreas defect due to insulin resistance. Increasing evidences support there are distinct degrees of subclinic inflammation in women with GDM and inflammation effect plays an important role in the process from insulin resistance to gestational diabetes mellitus[9]. There are several potential interpretations for this observation. First, mediators of inflammation in acute phase cause the elevation of productions released from adipose cells which induces insulin resistance. An alternate interpretation is that proinflammatory cytokine can affect signal conduction chain of insulin directly. A third interpretation is that lipoclasis mediated by proinflammatory cytokine promotes the liver to synthesize fatty acid straightly. Fourth, proinflammatory cytokine can mediate the damage of endothelial function. Finally, the decrease of IL-10 maybe contaminates endothelial function and signal conduction chain of insulin[10] . CRP as an important inflammatory factor , associated strictly with GDM, and the rise of serum CRP level also prog-nosticate the risk of type Ⅱ diabetes[11]. SHEN et al. demonstrated that intensive insulin therapy can effec-tively control the blood glucose and reduce serum CRP levels in newly onset diabetics receiving MDI or CSII regimen[12]. CRP does increase during the course of normal gestation. Recent researches find that pregnancy itself is an inflammatory state and serum CRP levels are raised as early as 4 weeks of gestation[13]. In our study, serum CRP levels and the leukocyte count in the GDM group were higher than those in the control group and serum C-reactive protein value correlated with serum glucose levels or the leukocyte count positively. The data indicate increased CRP levels were associated with an increased risk of developing GDM. Large researches demonstrates that obesity is an independent factor for the elevation of CRP and there is higher CRP level in those with abnormal glycometabolism[14]. There was a significant difference in both prepregnancy and preg-nancy BMI between the GDM group and the control group in our study, which demonstrate CRP is the risk indicator of GDM patient with obesity. HbA1c, reflect-ing the glucose mean level four or six weeks ago, which is not influenced by transient fluctuation of glucose concentration, is the index of diagnose and cure of GDM. HbA1c has an important reference value for the guide of treatment, determination of termination of pregnancy and evaluation of perinatal outcome of GDM. Our study demonstrated serum HbA1c level in GDM group was higher than that in NGT group($P < 0.05$) and had posi-tive correlation with CRP remarkably. The possible reason of the results is that hyperglycemia state of GDM patient can accelerate HbA1c' s formation and stimulate the expression of mononuclear macrophage and the release of inflammatory factors such as TNF-a, which leads to the elevation of CRP[15].

In a word, these observations highlight an important association between CRP and the development of GDM. The results of this study provide further support for the hypothesis that inflammation contributes to the development of glucose intolerance and CRP can act as the risk predictor of GDM. While regular postpartum GTT is universally recommended for the early diagnosis of diabetes in women with GDM, these results suggest that perhaps postpartum CRP screening might also play a role after pregnancy. The therapeutic regimen for this kind of patients should include combined therapy with anti-inflammatory effect, besides energetic alimentary control and regulation of blood glucose.

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·*Abstract*·

Translational research case studies: Development of antibodies for cancer diagnosis and therapy

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Antibodies are primary tools in several areas of biomedical sciences, including basic research, diagnostics, and molecular therapeutics. Antibodies are widely used in diagnostic applications for clinical medicine. Analysis of cells and tissues in pathology laboratories includes the use of antibodies on tissue sections. Further, antibodies are making rapid inroads into medical therapeutics, driven by technological evolution from chimeric and humanized to fully human antibodies. The therapeutic antibody market has the potential to reach $30 billion by 2010. Our lab has developed a monoclonal antibody, named Met4 that was raised against the extracellular domain of Met specifically with the goal of measuring Met in FFPE tissues. The Met receptor kinase is expressed on the cell surface of a significant number and variety of human primary solid tumors and in their metastases. The characterization of the Met4 antibody suggests it should possess adequate performance for quantification of Met expression in clinical specimens. We have also generated a fully human Fab fragment against EGFR; conjugated it to taxol as an immuno-chemotherapy agent; and investigated its in vitro anti-tumor efficacy on EGFR positive A431 epidermoid carcinoma cells. The Fab-Taxol conjugate inhibited A431 cell proliferation at low concentrations and in a dose-responsive manner; furthermore, almost 100% of cells underwent apoptosis after treatment with Fab-Taxol. Our findings suggest that this Fab-Taxol conjugate could be a potential immuno-chemotherapeutic drug for clinical treatment of EGFR over-expressing tumors.

Key words: monoclonal antibody; cancer diagnosis and therapy; Met 4